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COMPARING SINGLE AND CUMULATIVE DOSING PROCEDURES IN HUMAN TRIAZOLAM DISCRIMINATORS

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This study evaluated a cumulative dosing procedure for drug discrimination with human participants. Four participants learned to discriminate triazolam (0.35 mg/70 kg) from placebo. A crossover design was used to compare the results under a single dosing procedure with results obtained under a cumulative dosing procedure. Under the single dosing procedure, a dose of triazolam (0, 0.05, 0.15, or 0.35 mg/70 kg) or secobarbital (0, 25, 75, or 175 mg/70 kg) was administered 45 min before assessment. Determining each dose–effect curve thus required four sessions. Under the cumulative dosing procedure, four doses of triazolam (0, 0.05, 0.10, and 0.20 mg/70 kg) or secobarbital (0, 25, 50, and 100 mg/70 kg) were administered approximately 55 min apart, producing a complete dose–effect curve in one four-trial session. Regardless of procedure, triazolam and secobarbital produced discriminative stimulus and self-reported effects similar to previous single dosing studies in humans. Shifts to the right in cumulative dose–effect curves compared to single dose–effect curves occurred on several self-report measures. When qualitative stimulus functions rather than quantitative functions are of interest, application of cumulative dosing may increase efficiency in human drug discrimination.

Key words: cumulative dosing, drug discrimination, novel-response procedure, triazolam, secobarbital, subjective effects, humans

Drug discrimination studies with human participants often require a large number of sessions to complete. One method for increasing efficiency in human drug discrimination studies may be cumulative dosing (Boren, 1966). With a cumulative dosing procedure, incremental doses of a drug are administered across trials so that an entire dose–effect curve can be assessed in a single session. This procedure can substantially reduce the number of test sessions needed and has been successfully applied to studies of direct drug effects (e.g., effects on psychomotor performance) in humans and nonhumans, and to drug discrimination in nonhumans (Bickel et al., 1988; Clark, Schlinger, & Poling, 1990; de Wit, Dudish, & Ambre, 1993; Gui-Hua, Perry, & Woolverton, 1992; Melia & Spealman, 1991).

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An important first step in developing a cumulative dosing procedure for drug discrimination with human participants is to compare discriminative stimulus effects under a standard single dosing procedure and a cumulative dosing procedure. In nonhumans, several studies have compared the direct effects and discriminative stimulus effects from single and cumulative dosing procedures (Bertalmio, Herling, Hampton, Winger, & Woods, 1982; Sannerud & Ator, 1995; Terry, 1992; Thompson, Moerschbaecher, & Winsauer, 1983). With respect to drug discrimination studies comparing drug effects from both procedures, previous researchers have generally dichotomized between qualitative and quantitative similarities. *Qualitatively* similar effects result when both dosing procedures produce full generalization (i.e., ≥80% drug-appropriate responding); *quantitative* similarities occur when the slopes of dose–effect curves are equivalent (Bertalmio et al., 1982; Sannerud & Ator, 1995). Two studies that compared the discriminative stimulus effects of drugs across single and cumulative dosing procedures demonstrated qualitative comparability (Bertalmio et al., 1982; Sannerud & Ator, 1995), and hence, demonstrated the usefulness of cumulative dosing for drug discrimination research. Both studies reported some quantitative differences across pro-

cedures, with dose–effect curves shifted to the right under cumulative dosing. These quantitative differences have not prevented cumulative dosing procedures from being applied in nonhuman drug discrimination. Indeed, these procedures have been widely adopted for the study of discriminative stimulus effects in nonhumans (e.g., Clark et al., 1990; Gui-Hua et al., 1992; Melia & Spealman, 1991). In addition, cumulative dosing procedures have been used to investigate the antagonism of (France, Jacobson, & Woods, 1984; France & Woods, 1992; Massey, Vanover, & Woolverton, 1994; Peltier, Emmett-Oglesby, Thomas, & Schenk, 1994) and tolerance to (Pugh, Boone, & Emmett-Oglesby, 1992; Sannerud & Griffiths, 1993; Young, Kapitsopoulos, & Makhay, 1991) the discriminative stimulus effects of drugs.

To our knowledge, only two sets of experiments have compared single and cumulative dosing procedures in humans (Chait, Corwin, & Johanson, 1988; Chait, Evans, et al., 1988; de Wit et al., 1993). The first study compared the subjective and behavioral effects of orally administered diazepam given under single dosing with those under cumulative dosing that produced plasma levels of diazepam comparable to the single dosing procedure. Many of the subjective effects were qualitatively similar under both dosing procedures, but quantitatively greater self-reported (e.g., ratings of sedation) and behavioral (e.g., on psychomotor performance) effects occurred under single dosing (de Wit et al., 1993). In the second comparison, the subjective and behavioral effects of smoked marijuana were assessed under cumulative dosing (Chait, Corwin, & Johanson, 1988) and were compared to the effects from an earlier single dosing study from the same laboratory (Chait, Evans, et al., 1988). The effects on most physiological and subjective measures after cumulative dosing were qualitatively consistent with those previously reported from the same doses administered under single dosing. Quantitative differences occurred for heart rate, which was affected less by cumulative drug administration than by comparable single doses (Chait, Corwin, & Johanson, 1988).

The purpose of the present experiment was to evaluate a cumulative dosing procedure for human participants trained to discriminate triazolam from placebo. To understand the importance of elimination half-life to the effectiveness of cumulative dosing, the present study employed two drugs that differ on this dimension. Triazolam has a relatively short elimination half-life (2 to 5 hr; Harvey, 1980) compared to secobarbital (elimination half-life of 12 to 25 hr; Harvey, 1980). Substitution testing was conducted under a novel-response drug discrimination procedure, because in previous studies with humans trained to discriminate triazolam, the novel-response procedure has demonstrated increased selectivity of drug-appropriate responding compared to a standard two-response procedure (Kamien, Bickel, Smith, Higgins, & Badger, 1997). Responding on several self-report questionnaires also was assessed, because previous research suggests a strong correlation between drug discrimination responding and self-reported drug effects in humans (Preston & Bigelow, 1991).

METHOD

Participants

Participants were 3 male and 1 female (Participant 102) adult volunteers (ages 19 to 32 years), recruited through newspaper advertisements in local papers and posters, who provided written informed consent. All were in good health with no prior histories of psychiatric illness or drug or alcohol abuse according to medical histories provided by the participants, as well as physical assessments and routine laboratory screening. Current abstinence from amphetamine, barbiturates, benzodiazepines, cocaine, opioids, and cannabinoids was confirmed via urinalysis testing.

Participants 101 through 104 weighed 79.5, 54.5, 75, and 84.1 kg, respectively. None of the participants deviated by more than 10% from normal body weight (Metropolitan Life Insurance Company, 1983). All reported that they were light to moderate social drinkers (alcohol consumption of 3, 3, 6, and 5 drinks per week, respectively). Only Participant 102 reported current use of tobacco.

Participants were instructed to refrain from caffeine and solid food for 4 hr and alcohol for 24 hr prior to experimental sessions. Participants also were told to refrain from all il-

licit drug use for the duration of the study. Urine samples were obtained before each session, and a randomly selected sample for each subject was screened each week for cannabinoids and cocaine. For those participants with recent drug use (i.e., within the past 6 months) of other drug classes (e.g., barbiturates, opiates), urine screens included these classes of drugs in addition to cannabinoids and cocaine. A positive urine screen would have resulted in dismissal from the study. Pregnancy tests were completed for the female participant before each session.

Before each session, sobriety tests (i.e., tests of balance, hand coordination, and simple arithmetic) were completed as a baseline for comparison prior to release. Also before each session, blood pressure, breath alcohol levels, and heart rate were recorded to ensure a safe baseline for beginning the session.

Prior to release after each session, sobriety tests and a recall task were completed. Sobriety tests were repeated at 15-min intervals until participants did as well as, or better than, their performance when they arrived at the laboratory that morning. For the recall task, participants were told two three-syllable words and had to remember these words for 30 min. If participants failed to recall their words, they were told two additional words to remember for 30 min, and so on, until successful.

Participants received monetary compensation for their participation at the rate of $4 per hour and could obtain up to an additional $12 depending upon their performance each session.

Apparatus and Materials

The experiment was conducted in a room that contained eight experimental stations, separated by partitions. Each station had a comfortable chair, a computer monitor, and equipment for responding. All questionnaires and performance tests were presented on the computer monitor according to a timed sequence. Participants responded on a numeric keypad and on three buttons located on a separate apparatus. Commodore 64 microcomputers controlled stimulus presentations to the monitor and recorded data during each session.

Participants used the three buttons to respond to several self-report questionnaires. For all questionnaires, participants were told to respond to questions based on how they felt at the moment of answering the question. Self-report questionnaires were presented on the computer monitor and included the Addiction Research Center Inventory short form, which consists of 49 true-false questions that were scored as five subscales: a morphine-benzedrine group (MBG), a pentobarbital-chlorpromazine-alcohol group (PCAG), a lysergic acid diethylamide group (LSD), a benzedrine group (BG), and an amphetamine group (A) (Jasinski, 1977; Martin, Sloan, Shapiro, & Jasinski, 1971). Also included was the adjective rating scale, which presented 32 adjectives that participants rated on a 5-point scale from 0 (*not at all*) to 4 (*extremely*). The items from this scale were grouped into two subscales: a sedative scale consisting of adjectives describing sedative effects and a stimulant scale consisting of adjectives describing stimulant effects (Hughes et al., 1991). The final questionnaire was the visual analogue scales, which consisted of 100-point horizontal lines anchored with *not at all* on one end and *extremely* on the other. Participants rated the strength of drug effect, drug liking, good drug effects, bad drug effects, drug-induced high, drug-induced anxiety, the similarity of the drug to each training condition, and the similarity of the drug to a novel drug condition. The Digit Symbol Substitution Test was used to assess psychomotor performance (McLeod, Griffiths, Bigelow, & Yingling, 1982).

General Procedure

After an initial training session was conducted to familiarize participants with the computer tasks and the routine of the laboratory procedure, sessions were conducted three or four times per week. The study consisted of four phases: training, test of acquisition, a single dose testing phase, and a cumulative dose testing phase. Testing was conducted under both the single dosing and cumulative dosing procedures using a crossover design. Participants 101 and 104 completed the cumulative dose testing phase first, and Participants 102 and 103 completed the single dose testing phase first.

Sessions began at 9:00 a.m., and participants typically remained at the laboratory for 6 or 8 hr depending on the type of session

(see below). While in the laboratory, participants were told not to talk to one another and were monitored continuously throughout each session. First, a baseline assessment of dependent measures was conducted. These measures included the Addiction Research Center Inventory, the adjective rating scale, and the Digit Symbol Substitution Test. On the Digit Symbol Substitution Test, participants used a keypad to reproduce a geometric pattern associated with a digit according to the code presented continuously across the top of the screen. Participants were told to complete as many patterns as possible as accurately as possible in the allotted time (90 s). Data collected were the number of trials correctly completed and the total number of trials completed. Once these measures were completed, participants read their instructions (Appendix A). The blanks in these instructions were filled in with letter codes (e.g., A and B, C and D, etc.) that were counterbalanced across participants. Participants were then administered two capsules. Participants completed an assessment of dependent measures 45 min after capsule ingestion which included the Addiction Research Center Inventory, the adjective rating scale, the visual analogue scales, the Digit Symbol Substitution Test, and a discrimination task. The discrimination task was a Fixed-Interval (FI) 3-min schedule of point presentation in which subjects pressed a button associated with a drug code. The first response following each 1-s interval resulted in an increase of one point on the counter that was displayed on the monitor (i.e., a maximum of 180 points could be earned). A 10-s changeover delay arranged that no points could be delivered within 10 s of a switch from one letter code to another. Points earned on the capsule-appropriate code were converted into bonus earnings. Participants could earn a maximum of $3 or $12 for responding on the capsule-appropriate button (see below). The assessment of dependent measures required approximately 8 min to complete. A sealed envelope, which contained the letter code identity of the administered drug or the information that it was a test trial, was opened after the completion of the dependent measures. After either one or four trials of this type (see below), participants were released to a recovery area. In recovery, participants were free to snack, sleep, or engage in activities (e.g., watching TV) until their release times. Participant 102 was allowed to smoke during the recovery period. After a one-trial session, release procedures began at 2:30 p.m.; after a four-trial session, release procedures began at 4:00 p.m.

Design

Training phase. First, four one-trial training sessions were conducted in which participants received capsules containing either 0.35 mg/70 kg triazolam (e.g., Drug A) or placebo (e.g., Drug B). Participants were informed of the letter code appropriate for the drug at the time of drug administration (see Appendix A.1).

Test-of-acquisition phase. Next, the test-of-acquisition phase was conducted. Sessions consisted of one trial. Participants were not informed of the letter code associated with the administered drug so that discriminative control by the training stimuli could be tested (see Appendix A.2). In order to meet the criterion for acquisition of the discrimination, participants had to make ≥80% of their responses on the FI 1-s discrimination task on the capsule-appropriate button for four consecutive sessions within a maximum of eight total sessions. Participants who met this discrimination criterion were assigned to either the single or cumulative dose testing phase.

Single dose testing phase. Participants were informed that they could receive either training drug (e.g., Drug A or Drug B), or a novel drug, N, unlike either training drug (see Appendix A.3). Sessions consisted of one trial in which one dose of either triazolam (0, 0.05, 0.15, and 0.35 mg/70 kg) or secobarbital (0, 25, 75, and 175 mg/70 kg) was administered. The order of drug testing was mixed across participants. All doses of one drug were tested prior to testing the other drug. The order in which doses of each drug were tested was mixed within and across subjects. After completion of the dependent measures, participants were not informed of the letter code associated with the drug they received, but instead were informed at the end of the trial that they had completed a test trial. Participants were instructed that the accuracy of their responding would be disclosed at the completion of the study (Appendix A.3). In fact, participants were compensated $12 for

every test trial completed independent of their performance.

To ensure maintenance of discriminative control during testing, test-of-acquisition sessions were interspersed between test sessions. In these sessions, participants received either triazolam (0.35 mg/70 kg) or placebo. At the completion of the trial, the identity of the correct drug code was revealed. Participants had to meet the same criterion as in the test-of-acquisition phase (described above) to move to the next single dose test session. If they did not meet this criterion, additional test-of-acquisition sessions were added until performance in two consecutive sessions met the discrimination criterion.

Cumulative dose testing phase. Instructions during this phase were similar to those in the single dose test phase (see Appendix A.4). Sessions consisted of 4 trials. Successive doses of either triazolam (0, 0.05, 0.10, and 0.20 mg/70 kg, which resulted in cumulative doses of 0, 0.05, 0.15, and 0.35 mg/70 kg) or secobarbital (0, 25, 50, and 100 mg/70 kg, which resulted in cumulative doses of 0, 25, 75, and 175 mg/70 kg) were administered on different test sessions. The order of drug testing was mixed across participants. After the initial set of capsules was administered, additional capsules were administered following completion of the dependent measures and after the envelope had been opened, which resulted in an approximately 55-min interval between successive doses. At the end of each trial, participants were *not* informed of the letter code associated with the drug they received, but were instead informed that it was a test trial. Participants were told (see Appendix A.4) that the accuracy of their responding on test trials would be disclosed at the completion of the study. In fact, participants were compensated $3 for every test trial independent of their performance.

To ensure maintenance of discriminative control, test-of-acquisition sessions were interspersed between test sessions. In these sessions, participants received one triazolam trial (0.35 mg/70 kg) and three placebo trials in random order (i.e., triazolam-placebo-placebo-placebo; placebo-triazolam-placebo-placebo; placebo-placebo-triazolam-placebo; placebo-placebo-placebo-triazolam). Only those placebo trials administered before triazolam trials and triazolam trials served as test-of-acquisition trials (e.g., *placebo-placebo-triazolam*-placebo). Participants had to make ≥80% of their responses on the capsule-appropriate button for four consecutive test-of-acquisition trials in order to move to a cumulative test session. If they did not meet this criterion, additional test-of-acquisition sessions were added. At the completion of placebo trials that occurred before triazolam trials and after completion of triazolam trials (e.g., *placebo-placebo-triazolam*-placebo), participants were told either the letter code associated with the administered capsules or (falsely) that it was a test trial. This nonsystematic feedback was used to prevent control of responding by ordinal position. At the completion of a placebo trial occurring *after* the triazolam trial (e.g., placebo-placebo-triazolam-*placebo*) participants always were told that it was a test trial.

Drugs

Triazolam, placebo, and secobarbital were administered via two blue opaque capsules (Size 0) with approximately 175 ml of water. Capsules were prepared by the Medical Center Hospital of Vermont Pharmacy from triazolam (Upjohn) and secobarbital sodium (Sigma). Doses are expressed as the form of each drug used.

RESULTS

Data Analysis

Discrimination data are presented as the percentages of triazolam-appropriate and Novel responding on the FI 1-s discrimination measure for individual subjects. As with previous studies in human drug discrimination, the test capsule was considered to have substituted fully for the training dose when ≥80% of the total responses occurred on the appropriate key (Bickel, Oliveto, Kamien, Higgins, & Hughes, 1993; Kamien et al., 1997). The Addiction Research Center Inventory and the adjective rating scale scores are presented for individual participants as the change from baseline scores, and the results for the visual analogue scales and the Digit Symbol Substitution Test are the postdrug scores.

All 4 participants acquired the triazolam discrimination. Participants 101 and 102 each required eight sessions to meet the acquisi-

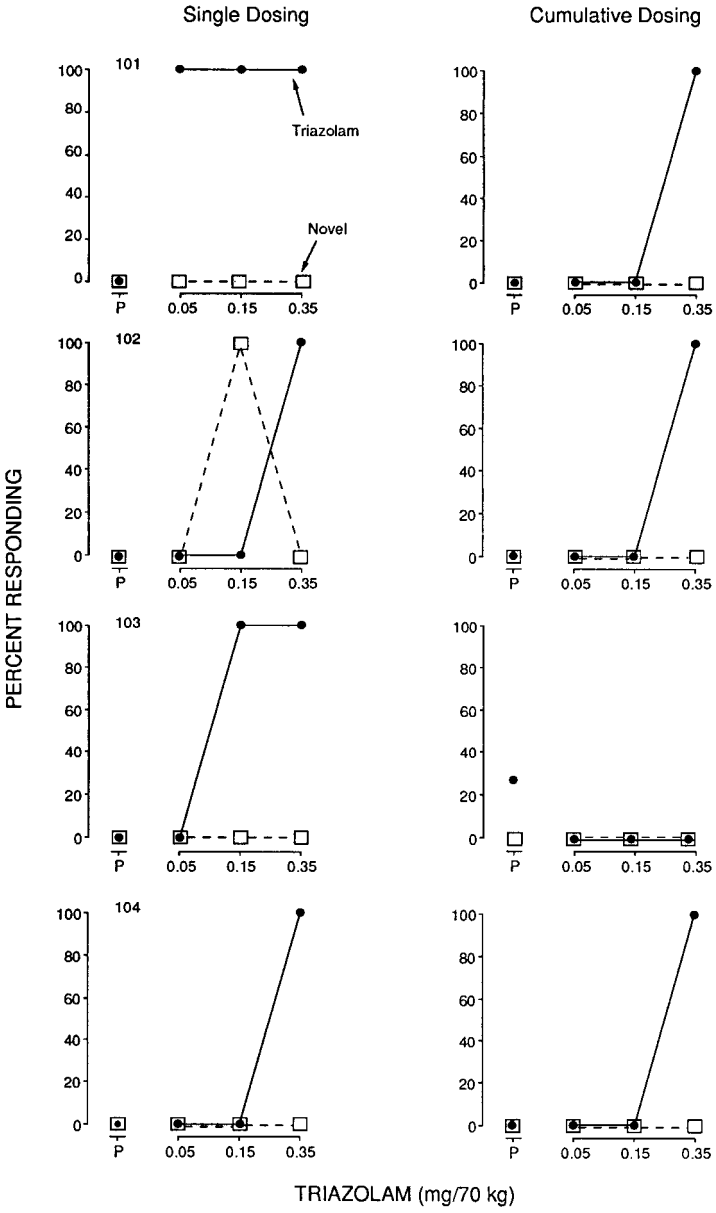

Fig. 1. Percentage of triazolam-appropriate (filled circles) and Novel responding (open squares) for each participant under the single (left panels) and cumulative (right panels) dosing procedures. Each point represents a single trial. Points above P indicate responding after placebo administration. The training dose of triazolam was 0.35 mg/70 kg.

tion criterion. and Participants 103 and 104 required four and seven sessions, respectively.

Discrimination Tests

Triazolam. Figure 1 shows the results of tests with triazolam under the single and cumulative dosing procedures for the 4 participants. Placebo produced 25% triazolam-appropriate responding in Participant 103 under the cumulative dosing condition and only placebo-appropriate responding in the remaining 3 participants under both dosing conditions. Participant 101 made the triazolam-appropriate response after every triazolam dose under

the single dosing procedure but did so only after the highest dose (0.35 mg/70 kg) under the cumulative dosing procedure. Participant 102 made the Novel response after 0.15 mg/70 kg triazolam under the single dosing procedure, but this dose occasioned placebo-appropriate responding under the cumulative dosing procedure. The highest dose (0.35 mg/70 kg) occasioned triazolam-appropriate responding under both dosing procedures in this participant. Participant 103 made the triazolam-appropriate response after the intermediate and high doses of triazolam under the single dosing procedure but not under the cumulative dosing procedure. Participant 104 responded identically under single and cumulative doses of triazolam, in that only 0.35 mg/70 kg occasioned triazolam-appropriate responding.

Overall, the single and cumulative dosing procedures produced the most similar discriminative stimulus effects after the highest dose of triazolam, with only 1 participant (103) showing a difference across dosing procedures at this dose. Greater variability in discriminative responding occurred after the intermediate dose, with 3 of 4 participants (101, 102, and 103) differing in their responses across the two dosing procedures.

Secobarbital. Figure 2 shows the results of substitution tests with secobarbital for the 4 participants. Secobarbital occasioned Novel responding at some dose under one or both dosing procedures for each participant. Participants 101 and 103 responded identically under both dosing procedures, with secobarbital occasioning Novel responding after all three doses (Participant 101) or after the two higher test doses (Participant 103). In contrast, for Participant 102, 75 mg/70 kg secobarbital occasioned triazolam-appropriate responding under the single dosing procedure but placebo-appropriate responding under the cumulative dosing procedure. After 175 mg/70 kg secobarbital, 80% and 100% Novel responding occurred under the single and cumulative dosing procedures, respectively. For Participant 104, 75 mg/70 kg secobarbital occasioned triazolam-appropriate responding under the single dosing procedure but Novel responding under the cumulative dosing procedure. As with Participant 102, 175 mg/70 kg secobarbital produced similar discriminative stimulus effects under both dosing procedures in Participant 104. However, unlike the other 3 participants, the highest secobarbital dose occasioned triazolam-appropriate rather than Novel responding.

Similar to the findings with triazolam, results were most consistent after the highest dose of secobarbital. Specifically, substitution profiles for the highest dose (175 mg/70 kg) were similar in all 4 participants under the single and cumulative dosing procedures. In contrast, at the intermediate dose, 2 participants (102 and 104) were inconsistent in their discriminated responding across procedures.

Self-Reports

The individual data from each self-report questionnaire are provided in Appendixes B through F. Appendixes include only data on measures demonstrating drug effects and those measures not represented in figures. The results from the self-report measures are described below across five distinct categories: (a) sedative scales, which include the PCAG subscale of the Addiction Research Center Inventory and the sedative subscale of the adjective rating scale; (b) stimulant or ''dysphoria'' scales, which include the LSD, BZ, and A subscales of the Addiction Research Center Inventory and the visual analogue scales that rate bad drug effects and drug-induced anxiety; (c) drug liking/''euphoria'' scales, which include the MBG subscale of the Addiction Research Center Inventory and the visual analogue scales that rate drug liking and good drug effects; (d) overall drug effect scales, which include the visual analogue scales rating drug-induced high and the strength of the drug effect; and (e) identification scales, which include the visual analogue scales rating the similarity of the test drug to triazolam, placebo, and the Novel drug.

Sedative Scales

Triazolam. As shown in Figure 3, triazolam produced dose-dependent increases on the PCAG subscale of the Addiction Research Center Inventory under both dosing procedures for 3 of the 4 participants. Two of these 3 participants (101 and 102) produced lower ratings under cumulative compared to single dosing; however, Participant 104 showed similar magnitudes of effects under both proce-

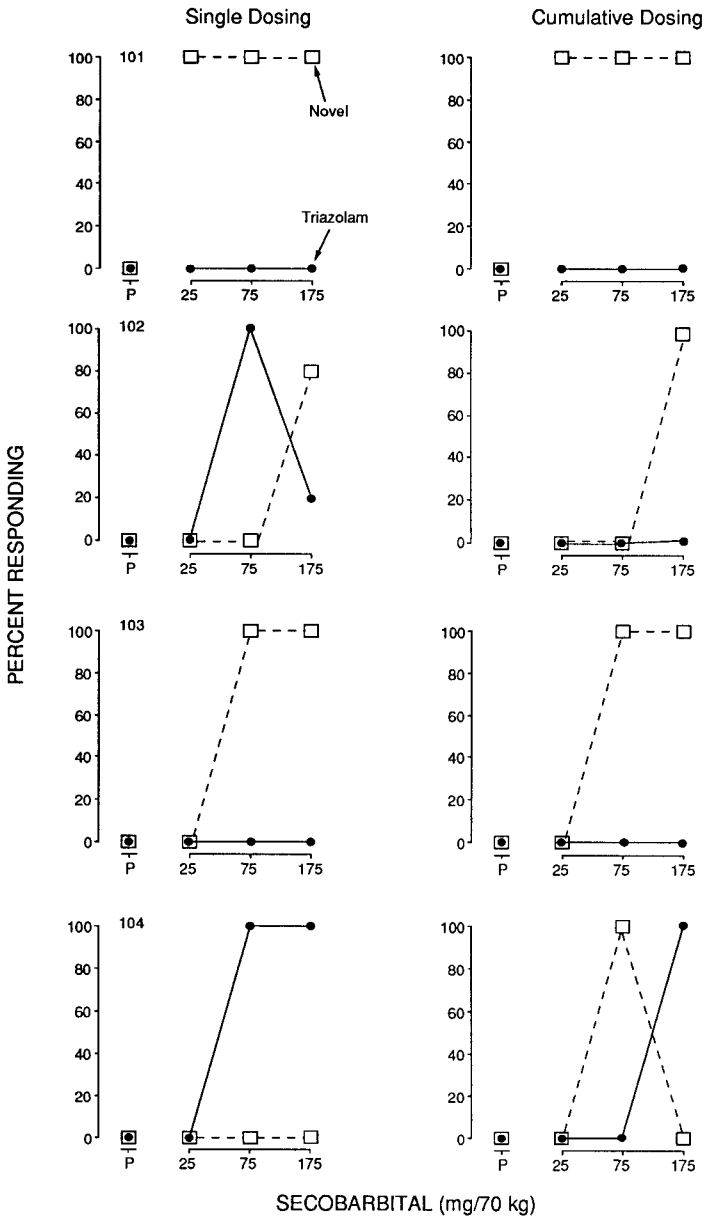

Fig. 2. Percentage of triazolam-appropriate and Novel responding to secobarbital for each participant. All else as in Figure 1.

dures (Figure 4). One participant (103) demonstrated dose-related increases on the PCAG subscale under the single but not the cumulative dosing procedure.

The sedative subscale (Appendix C) of the adjective rating scale resulted in similar effects as those of the PCAG. That is, Participant 103 showed dose-dependent increases on this scale under single but not under cumulative dosing, and the other participants showed dose-dependent increases under both procedures with a decreased magnitude of effects under the cumulative compared to the single dosing procedure.

Secobarbital. Secobarbital produced dose-dependent increases under both dosing procedures on the PCAG subscale of the Addiction Research Center Inventory in all 4 partici-

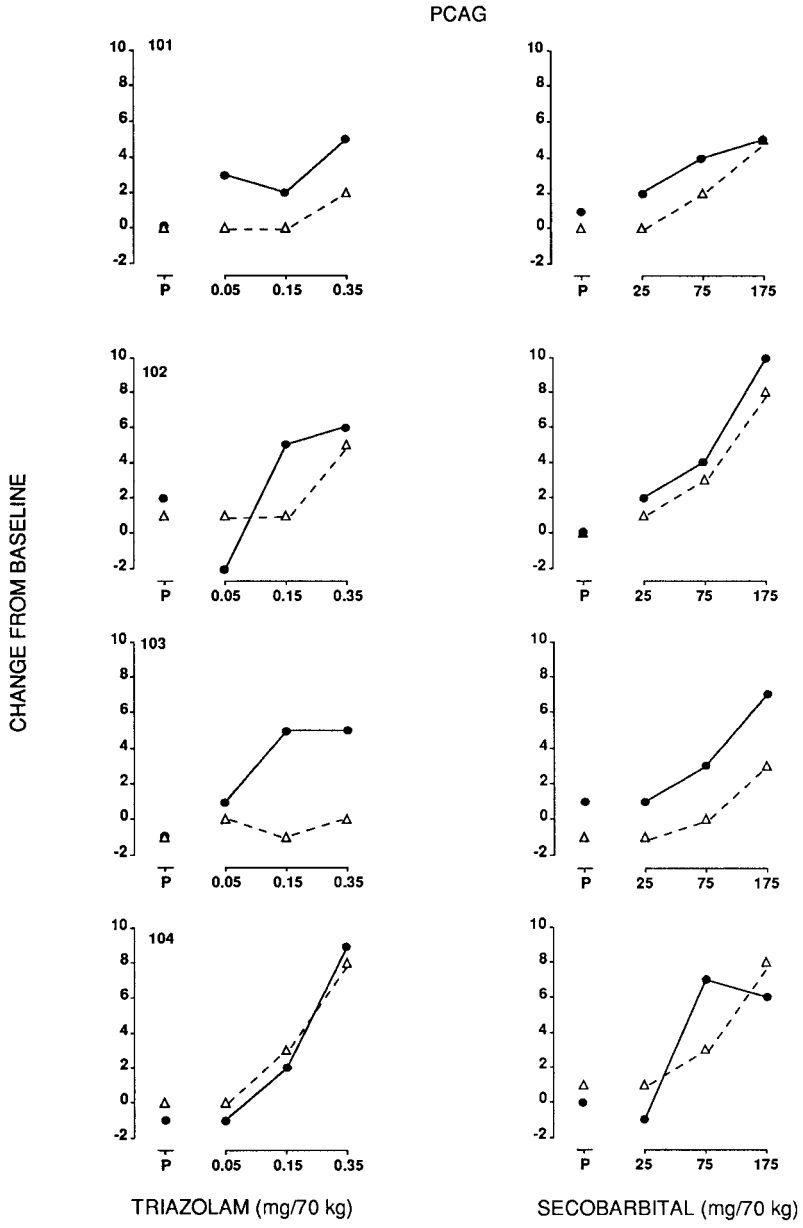

Fig. 3. Responding under the cumulative (triangles) and the single (circles) dosing procedures on the pentobarbital-chlorpromazine-alcohol group (PCAG) of the Addiction Research Center Inventory after triazolam (left panels) and after secobarbital (right panels) for each participant. Scores represent the change from baseline. All else as in Figure 1.

pants (Figure 3). For Participants 102 and 103, the magnitude of effects under cumulative dosing decreased compared to the effects under single dosing, but for Participants 101 and 104, the cumulative and single dosing procedures resulted in similar (101) or increased (104) effects after the highest test dose (Figure 3).

The pattern of effects on the sedative subscale of the adjective rating scale (Appendix C) was similar to that of the PCAG after secobarbital administration, in that each subject

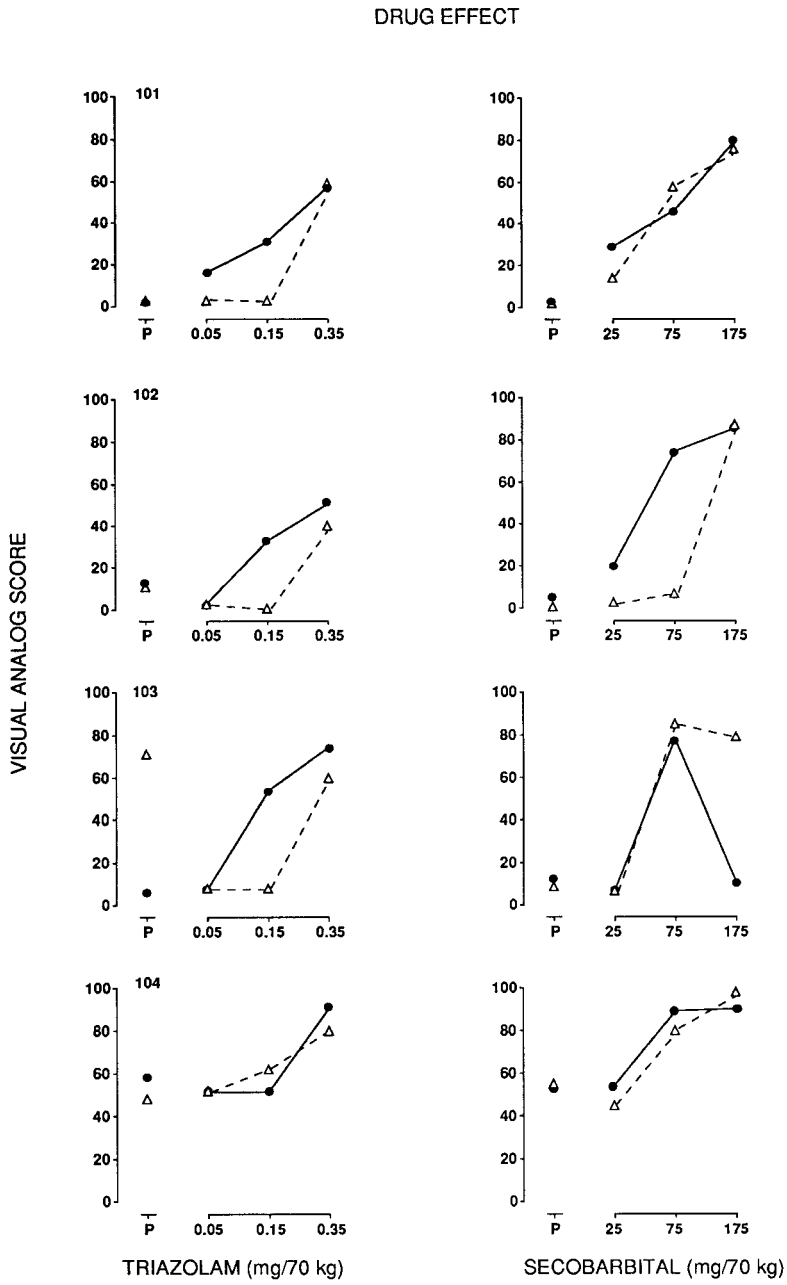

Fig. 4. Responding on the visual analogue scale rating the strength of drug effect. Scores represent the postdrug score. Triangles indicate results from the cumulative dosing procedure, and circles indicate results from the single dosing procedure. All else as in Figure 3.

showed dose-dependent increases after both dosing procedures; however, 2 participants (101 and 104) had greater magnitudes of effects under the cumulative dosing procedure than under the single dosing procedure.

Stimulant or "Dysphoria" Scales

Several scales sensitive to stimulant or dysphoric effects were not systematically affected by triazolam or secobarbital, regardless of

dosing procedure. These scales included the LSD, BG, and A subscales of the Addiction Research Center Inventory. The effects on the stimulant subscale of the adjective rating scale (not presented) were inconsistent across participants and dosing procedures.

Triazolam. The effects of triazolam on the stimulant subscale of the adjective rating scale were not consistent across participants. Participant 103 showed a dose-related decrease under the cumulative dosing procedure but not under the single dosing procedure. Participant 104 showed decreases under both dosing procedures. Triazolam did not produce clear dose-related changes in the other 2 participants.

In 1 participant (103), triazolam increased ratings of anxiety under both dosing procedures, although this effect was not dose dependent under single dosing. Other participants did not show increases on this measure.

Each participant reported dose-dependent increases on the visual analogue rating of bad drug effects (Appendix D) after triazolam administration, and these effects were not altered by dosing procedure.

Secobarbital. Secobarbital produced dose-related decreases under both procedures on the stimulant subscale of the adjective rating scale (not presented) in Participants 102 and 104. Participant 101 showed a similar decrease, but only under the single dosing procedure. In contrast, secobarbital occasioned a dose-dependent increase in stimulant ratings under both procedures in Participant 103.

Participant 101 reported dose-dependent increases on the anxiety rating after single but not after cumulative dosing with secobarbital. Other participants did not demonstrate increases or consistent results on this scale.

Secobarbital produced dose-related increases on the bad ratings under both dosing procedures, except that Participant 103 showed increased ratings under single but not under cumulative dosing.

Drug Liking/Euphoria Scales

Triazolam. No consistent dose-related increases occurred on the MBG subscale of the Addiction Research Center Inventory (Appendix B) after triazolam administration, although some evidence for dose-dependent decreases in Participants 101 and 104 was demonstrated.

The highest test dose of triazolam occasioned similar ratings of good drug effects (Appendix D) in Participant 101, regardless of dosing procedure, but Participant 103 demonstrated an increase only under the single dosing procedure. Participant 104 demonstrated a dose-dependent decrease on ratings of good drug effects under the cumulative but not under the single dosing procedure.

The measure of drug liking (Appendix D) showed similar results to the ratings of good drug effects.

Secobarbital. Secobarbital occasioned dose-dependent decreases on the MBG subscale of the Addiction Research Center Inventory in Participants 101 and 104, without clear differences by dosing procedure. Participant 102 did not demonstrate dose-related effects on this scale; however, a marginal increase in scores occurred for Participant 103 after cumulative administration of secobarbital.

Similar increases on ratings of good drug effects under both dosing procedures after secobarbital occurred in Participant 103. Participants 101 and 104 both showed dose-dependent increases on this measure; ratings were lower in magnitude under the cumulative compared to the single dosing procedure. A greater magnitude of effects under the cumulative compared to the single dosing procedure occurred in Participant 102.

The measure of drug liking occasioned similar results to the ratings of good drug effects.

Overall Drug Effect Scales

Triazolam. As shown in Figure 4, triazolam occasioned dose-dependent increases in ratings of strength of drug effect in all 4 participants. The magnitudes of these effects were lower under the cumulative dosing procedure compared to the single dosing procedure for Participants 102 and 103. For Participant 101, the magnitude of effects after the low and intermediate doses of triazolam were lower under the cumulative dosing procedure, but after the highest test dose, triazolam occasioned similar responses under both dosing procedures. For Participant 104, the effects were similar at each dose, but slightly lower under the cumulative compared to the single dosing procedure after the highest dose.

Ratings of drug-induced high (Appendix D) were similar to those of strength of drug effect.

Secobarbital. For Participants 101, 102, and 104, the results on ratings of strength of drug effect after secobarbital were similar to those from triazolam (Figure 4). Participant 103, however, had a decreased rating of drug effect after the highest test dose of secobarbital under the single dosing procedure but not under the cumulative dosing procedure.

Ratings of drug-induced high were similar to ratings of strength of drug effect, except for Participant 103 after single doses of secobarbital. In this case, the ratings were of similar magnitude as those under the cumulative dosing procedure.

Identification Scales

Triazolam. Triazolam produced dose-dependent increases on ratings of similarity to triazolam for all the participants after both dosing procedures (Appendix E). Dose-dependent decreases in the similarity of the test drug to placebo (Appendix E) occurred after triazolam for each participant except 102 under the cumulative dosing procedure. In this case, the highest dose of triazolam was identified as similar to placebo. Each participant, under at least one of the dosing procedures, demonstrated dose-related increases in rating triazolam as similar to a Novel drug (Appendix E).

Secobarbital. Secobarbital occasioned dose-dependent increases in rating the test drug as similar to triazolam in 3 of 4 participants (101, 102, and 104), with similar magnitudes of effects under both dosing procedures. In Participant 103, secobarbital did not occasion clear increases on this measure under either dosing procedure. Dose-dependent decreases in the similarity of the test drug to placebo occurred after secobarbital under both dosing procedures in each participant. Participants 101, 102, and 103 reported similar dose-related increases on ratings of similarity to a Novel drug after secobarbital under both dosing procedures. Participant 104, however, rated secobarbital (intermediate dose only) as similar to a Novel drug only under the cu mulative dosing procedure.

Digit Symbol Substitution Test

Triazolam. Both measures of Digit Symbol Substitution Test performance were affected by triazolam, regardless of dosing procedure. The number of total trials completed (Appendix F) as well as the number of trials correctly completed (Figure 5) were decreased by triazolam about equally under the cumulative and single dosing procedures for Participant 102. For Participant 101, the number of trials correctly completed decreased under both dosing procedures, but the total number of trials completed decreased relative to placebo only under the single dosing procedure. For Participants 103 and 104, although triazolam decreased scores dose dependently under both procedures, the effects under the cumulative dosing procedure were lower than the effects under the single dosing procedure.

Secobarbital. The effects of secobarbital on Digit Symbol Substitution Test performance were consistent with those effects observed after triazolam (Figure 5; Appendix F).

DISCUSSION

The present experiment evaluated a cumulative dosing procedure for drug discrimination with human participants by comparing the effects of single and cumulative doses of triazolam and secobarbital. For the majority of participants, the discriminative stimulus effects were qualitatively similar across dosing procedures. In several cases, quantitative differences occurred in which the dose–effect curve after cumulative dosing was shifted to the right compared to the dose–effect curve after single dosing. In general, the self-reported and performance effects were qualitatively similar, with some quantitative differences occurring as a function of dosing procedure.

The two dosing procedures produced discriminative stimulus effects similar to those reported in previous single dosing drug discrimination studies in which triazolam-placebo discriminations were trained in humans. The training dose (0.32 mg/70 kg) of triazolam, administered under standard single dosing conditions, occasioned between 80% and 100% triazolam-appropriate responding (Bickel et al., 1993; Kamien et al., 1994, 1997; Oliveto, Bickel, Hughes, Higgins, & Fenwick, 1992; Oliveto, Bickel, Kamien, Hughes, & Higgins, 1994). In the present study, the slightly higher training dose (0.35 mg/70 kg) occasioned an average of 75% and 100% tri-

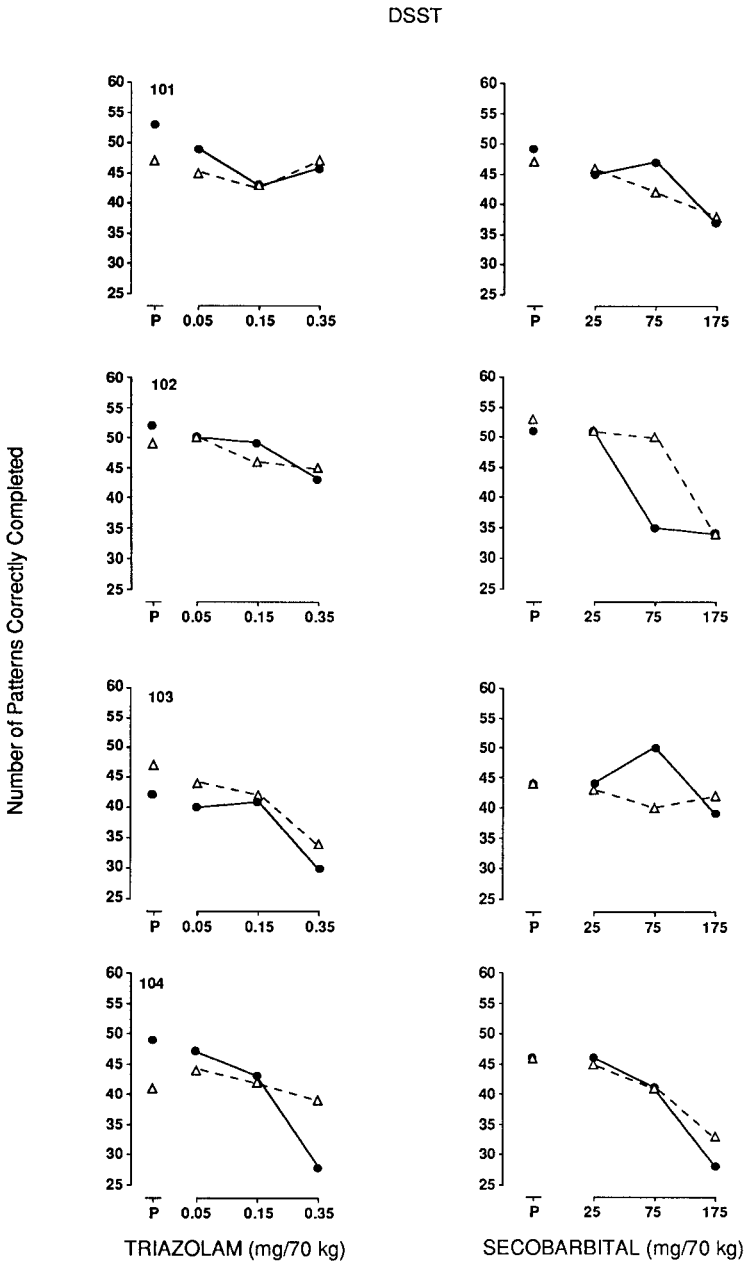

Fig. 5. Responding on the Digit Symbol Substitution Test. Triangles indicate results from the cumulative dosing procedure, and circles indicate results from the single dosing procedure. All else as in Figure 4.

azolam-appropriate responding under the cumulative and single dosing procedures, respectively. In addition, a prior study that trained humans to discriminate triazolam from placebo reported that secobarbital occasioned a mix of triazolam-appropriate and Novel responding (Kamien et al., 1997). In the present study, secobarbital also occasioned a mix of triazolam-appropriate and Novel responding under both the single and cumulative dosing procedures. Thus, the present results with triazolam and secobarbital were concordant with the results from previous single dosing studies.

To determine the qualitative similarity of results across dosing procedures, both the degree of generalization (responding to the triazolam-appropriate button given novel doses of drug) and the degree of Novel responding need to be assessed. The profiles of substitution after cumulative and single dosing were qualitatively similar for 3 of the 4 participants after triazolam. All other differences were quantitative, involving a shift to the right in the dose–effect curves after cumulative compared to single dosing. After secobarbital, 2 participants demonstrated qualitative differences across dosing procedures. For 1 participant (104) this involved responding on the Novel option under the cumulative but not under the single dosing procedure. Participant 102 responded on the triazolam-appropriate key after the intermediate dose of secobarbital under the single but not under the cumulative dosing procedure. The other 2 participants responded identically under both procedures. Thus, the results after triazolam demonstrated greater qualitative similarity than the results after secobarbital.

An alternative way to interpret the cumulative dosing results is to assess the final accumulation of drug and determine whether or not this ultimate dose is qualitatively comparable to the single dose. By this standard, the two dosing procedures resulted in nearly identical generalization profiles. That is, when the discriminative stimulus effects after the highest test doses are compared, only 1 participant demonstrated a qualitative difference in responding (Participant 103 after triazolam). However, this interpretation also suggests that the cases in which a cumulative dosing procedure would be appropriate are limited (e.g., when lowest discriminable doses are of interest).

The observed quantitative differences in the present study are consistent with the literature comparing cumulative and single dosing from drug discrimination with nonhuman subjects and studies of direct drug effects in nonhumans and humans (Bertalmio et al., 1982; Chait, Corwin, & Johanson, 1988; Chait, Evans, et al., 1988; de Wit et al., 1993; Sannerud & Ator, 1995; Terry, 1992; Thompson et al., 1983). The cumulative dosing procedure produced less quantitative attenuation of discriminative stimulus effects after secobarbital administration (one of four cases) than after triazolam administration (three of four cases).

The shifts to the right in dose–effect curves under the cumulative compared to the single dosing procedure may be due to at least two factors. First, the cumulative dosing session itself may not permit maximal drug accumulation. Recall that triazolam has a relatively shorter elimination half-life compared to secobarbital, yet both triazolam and secobarbital appear to be effective under the cumulative dosing procedure in that each generated dose-dependent increases in drug- or Novel-appropriate responding; however, as mentioned above, fewer quantitative differences occurred after secobarbital than after triazolam. Because the actual administered doses under the cumulative dosing procedure are lower than those of the single dosing procedure, maximal drug accumulation may not occur, because the effects of the previous dose may be decreasing by the time the next dose is administered. One way to overcome the problem of accumulating a drug with a shorter elimination half-life like triazolam may be to use slightly higher test doses under a cumulative dosing procedure in order to increase plasma levels to a level comparable to those of single doses (de Wit et al., 1993; Kaplan, Jack, Alexander, & Weinfeld, 1973) or to decrease the time interval between successive doses. On another pharmacokinetic dimension, triazolam and secobarbital reach peak plasma levels (i.e., time to maximum plasma level) at similar times (1.3 and 1.0 hr, respectively; Dalton, Martz, Rodda, Lemberger, & Forney, 1976; Eberts, Philopoulos, Reineke, & Vliek, 1981). In the present study, dependent measures were assessed 45 min after drug administration for both drugs. Thus, both drugs were assessed near peak plasma levels, suggesting that observed differences between these drugs are not a function of time to peak effect.

A second explanation for the quantitative difference between dosing procedures may be the development of acute tolerance. In fact, previous research comparing cumulative and single dosing procedures in humans found that even when each procedure resulted in equal plasma levels of diazepam, some self-reported and behavioral effects were decreased under the cumulative procedure compared to the single procedure (de Wit et

al., 1993). In the absence of measures of plasma levels, the influence of these factors (lack of accumulated drug and the development of acute tolerance) on the quantitative differences across procedures cannot be separated in the present study.

In several cases, but not all, self-report measures also demonstrated shifts to the right in the dose–effect curves generated under the cumulative dosing procedure compared to those generated under the single dosing procedure. These results are consistent with those from previous research in which diazepam was administered under both cumulative and single dosing procedures (de Wit et al., 1993). Diazepam increased ratings on scales such as the MBG and PCAG subscales of the Addiction Research Center Inventory under both dosing procedures, but the increases were greater in magnitude under single compared to cumulative dosing. In the present study, a similar trend was evident on several of the self-report measures; however, in fewer instances, the effects of triazolam and secobarbital after cumulative and single dosing were similar, and in a small number of cases, scores were actually more affected under cumulative than under single dosing. These differences across individuals and across measures in the present study may be due to various factors, such as individual differences in drug metabolism that may affect plasma levels or behavioral histories that may affect how individual participants respond to the self-report questions.

The present study employed several self-report measures that purportedly measure similar drug effects. For example, the PCAG subscale of the Addiction Research Center Inventory and the sedative subscale of the adjective rating scale have both been demonstrated to be sensitive to sedative drug effects (Bickel et al., 1993; Kamien et al., 1997). Indeed, in the present study, these scales were similarly affected by triazolam and secobarbital. In contrast, the MBG subscale of the Addiction Research Center Inventory, considered a measure of ''euphoria,'' did not result in responses similar to visual analogue scales that are purported to measure drug liking and ''good'' drug effects. Participants did not show any systematic effects on the MBG scale under either dosing procedure or for either drug. The other measures relating to positive mood effects were consistently affected by both triazolam and secobarbital, indicating that although participants may respond positively on these scales, they may not simultaneously endorse statements relating specifically to euphorigenic drug effects. This finding raises an interesting question in light of a previous study mentioned above (de Wit et al., 1993). In that study, diazepam occasioned relatively modest but reliable increases on the MBG for participants who reported moderate alcohol intake (six or more drinks per week) but who had no prior history of drug abuse. Participants in the present study had a similar history of light to moderate alcohol intake with no prior history of drug abuse. In addition, in our previous study (Kamien et al., 1997) that assessed the discriminative stimulus and self-reported effects of triazolam and secobarbital in a similar sample of participants, no significant increases on the MBG scale occurred after either triazolam or secobarbital. The different results across laboratories may be due to procedural factors such as the setting in which the study was conducted or to individual pharmacokinetic or behavioral differences.

In general, the self-reports that were sensitive to feelings of overall drug effects and sedative effects, as well as those that identified similarity to the training conditions or a novel condition, were well correlated with drug discrimination responding. These measures were typically sensitive to dose and demonstrated similar dose-related increases after triazolam and secobarbital. In addition, these results are consistent with those from a previous study of secobarbital's effects in participants discriminating triazolam from placebo (Kamien et al., 1997).

In terms of the relationship between self-reported drug effects and discrimination responding, both the previous study with secobarbital and the present study suggest that secobarbital can be distinguished from triazolam based on discrimination responding under the Novel-response procedure but not based on responses to the self-report measures. Thus, the drug discrimination measure appears to have greater selectivity than the drug self-report measures used in this study. This conclusion is consistent with results from a three-choice procedure with nonhuman subjects, which demonstrated that barbiturates and benzodiaze-

pines can be differentiated (Sannerud & Ator, 1995) and with recent research on human drug discrimination that demonstrated that three-choice procedures permit finer distinctions to be made among drugs than either self-report measures or standard two-choice drug discrimination procedures (e.g., Preston, Bigelow, Bickel, & Liebson, 1989).

Two potential problems that may limit the generality of results from this study are that only one assessment was made at each dose for each subject and that a four-placebo control session was not conducted. The greatest benefit of developing a viable cumulative dosing procedure for human drug discrimination would be to reduce the large number of sessions necessary to complete studies. Future studies that apply this procedure may therefore be in a position to conduct double determinations within participants without the concern of participant retention. Also, a control condition in which participants were given four consecutive placebo doses would have controlled for the possibility that participants switched from the placebo to an active drug button merely as a function of time in the session.

An important aspect of the present study is that it represents a first step in the development of a cumulative dosing procedure for drug discrimination with human participants. As such, although the quantitative differences between dosing procedures did occur, the overall qualitative similarity between dosing procedures may be of most interest when considering further development and application of cumulative dosing in drug discrimination research. Indeed, future research may focus on methods for reducing such quantitative differences, as discussed above. If used appropriately, a cumulative dosing procedure for drug discrimination with human participants should not only enhance experimental efficiency but also provide a method for exploring more complex issues in human drug discrimination that are currently not possible due to the time restrictions imposed by single dosing procedures.

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APPENDIX A

Instructional Sets

1. Training Instructions

For this part of the experiment, you will be administered one of two drugs, either _ or _. You will be immediately told which drug you are receiving. After the drug is administered, you will complete the computer tasks according to which drug you received. In proceeding with the computer tasks, you have the opportunity to make one of three responses for indicating the drug you received. Use the left button to indicate drug _ and the middle button to indicate drug _. The right button (N) can be used to indicate a drug that is not precisely like either _ or _. At the end of the session you will earn up to $12.00 depending upon your performance during the tasks.

2. Test-of-Acquisition Instructions

For this part of the experiment, you will be administered one of two drugs, either _ or _ without being informed of which drug you are receiving. After the drug is administered, you will complete the computer tasks and indicate which drug you received. In proceeding with the computer tasks, you have the opportunity to make one of three responses for indicating the drug you think you received.

Use the left button to indicate drug __ and the middle button to indicate drug __. The right button (N) can be used to indicate a drug that is not precisely like either __ or __. You will complete from one to four trials in each session. At the end of the session you will be told which drug you received. If you indicated correctly, you will earn up to $12.00.

3. Single Dosing Test Phase

For this part of the experiment, you may have a __ day, a __ day or a test day. On a test day, the drug you receive may be precisely __, precisely __ or may not be precisely like __ or __. You will not be given any information at the beginning of the session to indicate which drug you received, or if it is a test day. You will proceed with the computer tasks and indicate which drug you received. Use the left button to indicate drug __, the middle button to indicate drug __ and the right button (N) when you beleive the drug is not precisely like __ or __. At the end of the session, you will be told which drug you received or whether it was a test day.

BONUS: If you had a test day and the drug was __ or __ you will earn the average amount you received on the last four __ and __ days only if you responded on either the __ or __ buttons. If it was a test day and the drug you received was neither __ nor __, then you will earn the amount you responded on the __ button. On every test day you will not be told whether you received __, __, or __ until the end of the study. Thus, you will not be told how much you earned on each test day until the study is completed.

4. Cumulative Dosing Test Phase

For this part of the experiment, you will complete four trials each session. For each trial, you may have a __ trial, a __ trial or a test trial. On a test trial, the drug you receive may be precisely __, precisely __ or may not be precisely like __ or __. You will not be given any information at the beginning of a trial to indicate which drug you received, or if it is a test trial. You will proceed with the computer tasks and indicate which drug you received. Use the left button to indicate drug __, the middle button to indicate drug __ and the right button (N) when you believe the drug is not precisely like __ or __. At the end of each trial, you will be told which drug you received or if it was a test trial.

BONUS: If you had a test trial and the drug was __ or __ you will earn the average amount you received on the last four __ and __ trials only if you responded on either the __ or __ buttons. If it was a test trial and the drug you received was neither __ nor __, then you will earn the amount you responded on the __ button. On every test trial you will not be told whether you received __, __, or __ until the end of the study. Thus, you will not be told how much you earned on each test trial until the study is completed.

APPENDIX B

Change from baseline scores subscales of the Addiction Research Center Inventory under cumulative (C) and single (S) dosing.

		BG		MBG	
Participant	Dose	C	S	C	S
Triazolam					
101	Placebo	0	0	0	−1
	0.05	0	−1	0	−4
	0.15	0	−1	0	0
	0.35	−2	−2	−5	−4
102	Placebo	0	−1	0	−1
	0.05	0	1	0	1
	0.15	0	−3	0	0
	0.35	−5	−2	0	1
103	Placebo	0	0	0	0
	0.05	0	0	0	−1
	0.15	1	0	1	0
	0.35	0	−2	0	−1
104	Placebo	1	1	0	0
	0.05	1	0	0	0
	0.15	0	0	−3	−2
	0.35	−1	0	−1	−6
Secobarbital					
101	Placebo	0	0	0	1
	25	0	0	0	−4
	75	−1	−3	−4	−5
	175	−3	−2	−7	−5
102	Placebo	0	0	0	0
	25	−1	−1	−1	−1
	75	−2	−4	−1	0
	175	−6	−6	−1	−1
103	Placebo	1	−1	1	−1
	25	1	0	1	−1
	75	0	−2	2	1
	175	0	−2	3	0
104	Placebo	−3	−1	−1	−1
	25	−2	1	−1	0
	75	−2	0	−2	−1
	175	−2	−4	−5	−4

Note. The benzedrine group (BG; possible raw scores: 0 to 13) is sensitive to stimulant effects; the morphine-benzedrine group (MBG; 0 to 11) is sensitive to euphoric effects.

APPENDIX C

Change from baseline scores on the sedative subscale of the Adjective Rating Scale under cumulative (C) and single (S) dosing.

		Sedative subscale	
Participant	Dose	C	S
Triazolam			
101	Placebo	0	0
	0.05	0	1
	0.15	0	0
	0.35	1	3
102	Placebo	1	6
	0.05	0	−5
	0.15	1	11
	0.35	11	13
103	Placebo	−7	0
	0.05	−4	−3
	0.15	−8	5
	0.35	−4	2
104	Placebo	0	1
	0.05	2	1
	0.15	1	1
	0.35	8	11
Secobarbital			
101	Placebo	0	0
	25	0	2
	75	1	1
	175	7	2
102	Placebo	2	1
	25	1	10
	75	7	27
	175	30	34
103	Placebo	−2	−6
	25	−3	1
	75	−1	9
	175	1	9
104	Placebo	2	1
	25	1	0
	75	6	7
	175	22	9

Note. Raw scores on this subscale can range from 0 to 64.

APPENDIX D

Postdrug scores on the 100-point visual analogue scales relating to drug effects under cumulative (C) and single (S) dosing.

		Drug effect		Drug liking		Good effects		Bad effects		Drug-induced high	
Participant	Dose	C	S	C	S	C	S	C	S	C	S
Triazolam											
101	Placebo	3	2	45	36	3	4	3	2	2	2
	0.05	3	16	43	20	4	17	1	13	1	13
	0.15	3	31	44	26	1	38	4	17	2	21
	0.35	59	57	35	31	51	48	52	26	36	47
102	Placebo	11	13	2	8	0	5	1	5	2	5
	0.05	3	3	2	5	0	5	1	3	1	3
	0.15	1	33	2	52	2	51	2	32	4	39
	0.35	40	51	21	7	18	7	18	7	48	50
103	Placebo	71	6	7	10	8	11	7	10	6	10
	0.05	8	8	7	7	8	8	6	11	5	8
	0.15	8	54	7	52	4	53	6	54	4	35
	0.35	60	74	11	52	13	58	13	29	43	66
104	Placebo	48	58	77	49	51	41	4	31	26	46
	0.05	52	52	52	50	29	38	2	14	37	25
	0.15	62	52	50	61	29	44	3	22	31	53
	0.35	80	91	10	81	9	53	72	30	65	94
Secobarbital											
101	Placebo	2	3	44	47	3	2	2	2	3	4
	25	14	29	45	20	8	27	10	20	10	14
	75	58	46	24	34	16	42	28	38	33	33
	175	76	80	9	40	22	52	30	45	38	66
102	Placebo	1	5	3	6	2	3	1	4	1	6
	25	3	20	4	8	1	7	3	7	3	8
	75	7	74	5	45	5	45	4	14	7	48
	175	87	86	50	30	52	29	26	34	78	85
103	Placebo	9	12	3	6	5	8	6	7	4	6
	25	7	7	5	8	5	5	6	8	5	6
	75	85	77	82	64	76	70	6	10	46	64
	175	79	11	0	77	75	78	6	53	76	73
104	Placebo	55	54	68	51	3	35	4	4	16	19
	25	45	54	53	53	15	35	2	26	43	32
	75	80	89	69	58	4	53	28	31	37	76
	175	98	90	2	46	3	28	80	66	73	81

APPENDIX E

Postdrug scores on the 100-point visual analogue scales relating to drug identification under cumulative (C) and single (S) dosing.

Participant	Dose	Similar to placebo		Similar to triazolam		Similar to novel	
		C	S	C	S	C	S
Triazolam							
101	Placebo	93	82	3	2	1	3
	0.05	97	26	2	42	3	4
	0.15	92	4	2	89	2	50
	0.35	2	2	96	99	83	62
102	Placebo	97	96	10	13	12	13
	0.05	100	99	1	5	0	4
	0.15	97	66	6	46	6	48
	0.35	75	9	75	88	81	67
103	Placebo	82	15	11	11	5	23
	0.05	82	75	5	10	11	6
	0.15	71	14	5	64	4	51
	0.35	8	12	74	75	9	71
104	Placebo	100	95	2	0	2	4
	0.05	94	100	3	0	5	0
	0.15	89	94	3	2	7	8
	0.35	5	2	95	95	56	4
Secobarbital							
101	Placebo	100	100	1	1	2	1
	25	1	2	15	48	31	61
	75	0	2	31	34	49	63
	175	2	1	59	42	69	68
102	Placebo	100	92	20	4	23	6
	25	83	84	8	28	12	15
	75	94	2	3	88	4	54
	175	1	3	65	80	99	90
103	Placebo	82	79	8	7	6	7
	25	72	68	4	7	5	5
	75	6	4	6	5	82	80
	175	6	9	6	10	81	93
104	Placebo	97	83	1	1	2	5
	25	93	100	1	1	3	3
	75	8	0	75	94	98	4
	175	3	2	93	93	1	2

APPENDIX F

Postdrug scores on both measures of DSST performance under cumulative (C) and single (S) dosing.

Participant	Dose	Number completed	
		C	S
Triazolam			
101	Placebo	47	57
	0.05	45	54
	0.15	49	47
	0.35	47	47
102	Placebo	52	55
	0.05	52	55
	0.15	48	50
	0.35	45	44
103	Placebo	47	42
	0.05	46	40
	0.15	44	41
	0.35	40	33
104	Placebo	42	49
	0.05	44	47
	0.15	42	43
	0.35	39	32
Secobarbital			
101	Placebo	47	51
	25	48	51
	75	48	53
	175	40	43
102	Placebo	53	52
	25	52	52
	75	52	47
	175	42	43
103	Placebo	48	44
	25	46	45
	75	46	50
	175	45	39
104	Placebo	46	46
	25	45	46
	75	41	42
	175	33	32